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SEARCH REQUEST FORM

Requester's Full Name: Robert (Kathy) Shiao Examiner #: 7954 Date: 11/21/05

Art Unit: 1626 Phone Number: 2-0707 Serial Number: 10/628,649

Location (Bldg/Room#): KEM (Mailbox #): 5A10/ 5C18 Results Format Preferred (circle): PAPER DISK

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Acyl phosphate inhibitor of beta-

Inventors (please provide full names): Besterman et al

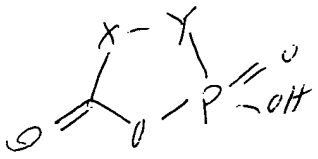
Earliest Priority Date: _____

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

I. Search cpd I (see claim 5) X is C, i.e. alkylene, cycloalkylene, heterocycle heterocycle.



Y is O, or C.

II Search cpds of claim 22

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Date Searcher Picked Up: 12/8/05

Date Completed: 12/8/05

Searcher Prep & Review Time: 15

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Type of Search

_____ NA Sequence (#)

_____ AA Sequence (#)

✓ Structure (#)

_____ Bibliographic

_____ Litigation

_____ Fulltext

_____ Other

Vendors and cost where applicable

✓ STN _____ Dialog

_____ Questel/Orbit _____ Lexis/Nexis

_____ Westlaw _____ WWW/Internet

____ In-house sequence systems

____ Commercial ____ Oligomer ____ Score/Length

____ Interference ____ SPDI ____ Encode/Transl

_____ Other (specify)

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 172095

TO: Rei-Tsang Shiao Location: 5a10 / 5c18 Thursday, December 08, 2005 Art Unit: 1626 Phone: 571-272-0707 Serial Number: 10 / 628649	From: Jan Delaval Location: Biotech-Chem Library Remsen 1a51 Phone: 571-272-2504 jan.delaval@uspto.gov

Search Notes

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Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact:***

Mary Hale, Information Branch Supervisor
22507, Remsen 1d86

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- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
  (journal articles, conference proceedings, new product announcements etc.)

- *Relevant prior art **not found:***
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

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L13              STR
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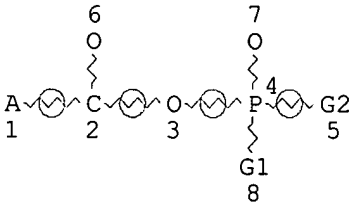


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VAR G2=C/O
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS   8

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED    2685 ITERATIONS                          197 ANSWERS
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L2             2 S (US2003-628649# OR US2001-797308# OR US2000-582255# OR WO98-U
L3             2 S L1,L2
               E BESTERMAN J/AU
L4            75 S E3-E8,E11
               E RAHIL J/AU
L5            24 S E3-E6
               E PRATT R/AU
L6           520 S E3-E28
               E PRATT REX/AU
L7            11 S E3,E4
               E METHYLGENE/PA,CS
L8            38 S E3-E10
               E METHYL GENE/PA,CS
               SEL RN L3

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L9            67 S E1-E67
L10            1 S 9073-60-3
L11           60 S L9 AND P/ELS
L12            6 S L11 AND (OPOC3 OR OPOC3-C6)/ES
L13              STR
L14           10 S L13
L15          197 S L13 FUL
               SAV TEMP L15 SHIAO628/A
L16           64 S L15 AND (OPOC3 OR OPOC3-C6)/ES
L17           64 S L12,L16
L18          133 S L15 NOT L17
L19           25 S L18 AND (C3H5O4P OR C8H4O8P2 OR C3H3O5P OR C10H9O4P OR C8H7O4
L20           24 S L19 NOT C6-C6/ES
L21           16 S L17 AND (C7H4BRO4P OR C9H6O5P OR C5H7O6P OR C9H9O5P OR C7H4O5
L22           14 S L21 NOT (13237-77-9 OR 13237-77-9/CRN)
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L24           38 S L20,L22,L12
               SAV TEMP L24 SHIAO628A/A

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L25           10 S L24
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               EDIT E68-E77 /AN /OREF

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L26           19 S E68-E77
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L28           39 S L24
L29            6 S L3-L8 AND L27,L28
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L30       10678 S L10
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L32        3644 S PENICILLINASE
L33           6 S L27,L28 AND L30-L32
L34           6 S L29,L33
L35          29 S L28 AND (PY<=1997 OR PRY<=1997 OR AY<=1997)
L36           7 S L27 AND L35
L37          11 S L27,L36
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L39           0 S L38 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
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L41           7 S L24(L)(THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L42           2 S L41 AND L35
L43           7 S L34,L40,L42
L44           2 S L24 AND BIOL+NT/RL AND L35
L45           7 S L43,L44
L46           7 S L45 AND L1-L8, L26-L45
L47           3 S L46 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
L48           6 S L46 AND L24(L)(THU OR BAC OR PKT OR PAC OR DMA OR BIOL)/RL
L49           7 S L46-L48

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L49  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:376963  HCAPLUS
DN   141:102080
ED   Entered STN:  11 May 2004
TI   Toward Better Antibiotics: Crystallographic Studies of a Novel Class of
     DD-Peptidase/β -Lactamase Inhibitors
AU   Silvaggi, Nicholas R.; Kaur, Kamaljit; Adediran, S. A.; Pratt, R.
     F.; Kelly, Judith A.
CS   Department of Molecular and Cell Biology and Institute for Materials
     Science, University of Connecticut, Storrs, CT, 06269-3125, USA
```

SO Biochemistry (2004), 43(22), 7046-7053
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): **1**

AB β-Lactam antibiotics are vital weapons in the treatment of bacterial infections, but their future is under increasing threat from **.beta .-lactamases**. These bacterial enzymes hydrolyze and inactivate β-lactam antibiotics, rendering the host cell resistant to the bactericidal effects of the drugs. Nevertheless, the bacterial D-alanyl-D-alanine transpeptidases (DD-peptidases), the killing targets of β-lactams, remain attractive targets for antibiotic compds. Cyclic acyl phosph(on)ates have been developed and investigated as potential inhibitors of both transpeptidases and β **-lactamases**. The x-ray crystal structures of the complexes of the Streptomyces strain R61 DD-peptidase inhibited by a bicyclic [1-hydroxy-4,5-benzo-2,6-dioxaphosphorinanone(3)-1-oxide] and a monocyclic [1-hydroxy-4-phenyl-2,6-dioxaphosphorinanone(3)-1-oxide] acyl phosphate were determined to investigate the mode of action of these novel inhibitors. The structures show, first, that these inhibitors form covalent bonds with the active site serine residue of the enzyme and that the refractory complexes thus formed are phosphoryl-enzyme species rather than acyl enzymes. The complexes are long-lived largely because, after ring opening, the ligands adopt conformations that cannot directly recyclize, the latter a phenomenon previously observed with cyclic acyl phosph(on)ates. While the two inhibitors bind in nearly identical conformations, the phosphoryl-enzyme complex formed from the monocyclic compound is significantly less mobile than that formed from the bicyclic compound Despite this difference, the complex with the bicyclic compound breaks down to regenerate free enzyme somewhat more slowly than that of the monocyclic. This may be because of steric problems associated with the reorientation of the larger bicyclic ligand required for reactivation. The structures are strikingly different in the orientation of the phosphoryl moiety from those generated using more specific phosph(on)ates. Models of the noncovalent complexes of the monocyclic compound with the R61 DD-peptidase and a structurally very similar class C β **-lactamase** suggest reasons why the former enzyme is phosphorylated by this compound, while the latter is acylated. Finally, this paper provides information that will help in the design of addnl. DD-peptidase inhibitors with the potential to serve as leads in the development of novel antibiotics.

ST DD peptidase lactamase inhibitor crystal structure antibiotic design; dioxaphosphorinanone oxide inhibitor DD peptidase crystal structure

IT Enzyme functional sites
(active; crystal structure of DD-peptidase/β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Chemical engineering design
(biochem. engineering design; crystal structure of DD-peptidase/ β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Conformation
Crystal structure
Molecular modeling
Streptomyces
(crystal structure of DD-peptidase/β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT Lactams
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, antibiotics; crystal structure of DD-peptidase/ β

-lactamase inhibitor complexes in relation to antibiotic design)

IT Antibiotics
(β-lactam; crystal structure of DD-peptidase/ β - **lactamase** inhibitor complexes in relation to antibiotic design)

IT 56-45-1, L-Serine, biological studies **9073-60-3**, β **-Lactamase** 9077-67-2D, complexes with dioxaphosphorinanone oxides
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(crystal structure of DD-peptidase/β **-lactamase** inhibitor complexes in relation to antibiotic design)

IT **91746-64-4D**, complexes with DD-peptidase **717919-90-9D**, complexes with DD-peptidase
RL: BSU (Biological study, unclassified); PRP (Properties); **BIOL (Biological study)**
(inhibitor; crystal structure of DD-peptidase/β - **lactamase** inhibitor complexes in relation to antibiotic design)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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OS CASREACT 138:233885

AB The cyclic acyl phosph(on)ates, 1-hydroxy-5-phenyl-2,6-dioxaphosphorinone(3)-1-oxide, its 4-Ph isomer, and the phosphonate (2-oxo) analog of the latter inhibited typical class A (TEM-2) and class C (Enterobacter cloacae P99) β **-lactamases** in a time-dependent fashion. No enzyme-catalyzed turnover was detected in any case. The interactions occurring were interpreted in terms of the reaction scheme E + I .rdblhar. EI .rdblhar. EI', where EI is a reversibly formed noncovalent complex, and EI' is a covalent complex. Reactions of the cyclic phosphates with the P99 β **-lactamase** were effectively irreversible, while that of the 4-Ph cyclic phosphate with the TEM β **-lactamase** was slowly reversible. The 4-Ph cyclic phosphate was generally the most effective inhibitor, both kinetically and thermodynamically, with second-order rate consts. of inactivation of both enzymes around 104 s-1 M-1. This compound also bound noncovalently to both enzymes, with dissociation consts. of 25 μM from the P99 enzyme and 100 μM from the TEM. It is unusual to find an inhibitor equally effective against the TEM and P99 enzymes; the β **-lactamase** inhibitors currently employed in medical practice (e.g., clavulanic acid) are significantly more effective against class A enzymes. The results of lysinoalanine anal. after hydroxide treatment of the inhibited enzymes and of a 31P NMR spectrum of one such complex were interpreted as favoring a mechanism of inactivation by enzyme acylation rather than phosphylation. Mol. modeling of the enzyme complexes of the 4-Ph phosphate revealed bound conformations where recyclization and thus reactivation of the enzyme would be difficult. The compds. studied were turned over slowly or not at all by acetylcholinesterase and phosphodiesterase I.

ST lactamase inactivation monocyclic acyl phosphate active site serine

IT Acylation
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT Enzyme functional sites
(inhibitor-binding; monocyclic acyl phosph(on)ates can acylate serine residue at active site of P99 and TEM-2 β **-lactamase** for its inhibition)

IT Enzyme kinetics
(of inhibition; kinetic parameters of P99 and TEM-2 β **-lactamases**)

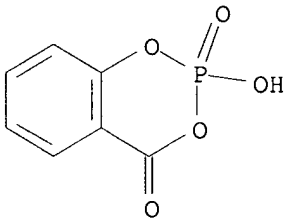
IT 56-45-1, L-Serine, biological studies **9073-60-3**, β **-Lactamase 27238-11-5 91746-64-4 229344-36-9**
RL: BSU (Biological study, unclassified); **BIOL (Biological study)**
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT **501948-95-4P 501948-97-6P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT 90-27-7, 2-Phenyl butanoic acid 101-97-3, Ethyl phenylacetate 109-94-4, Ethyl formate 119-43-7, Ethyl 2-phenyl butanoate 122-52-1 128-08-5, N-Bromosuccinimide 814-49-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)

IT **9073-60-3, β -Lactamase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(crystal structure of DD-peptidase/β **-lactamase** inhibitor complexes in relation to antibiotic design)
RN 9073-60-3 HCAPLUS
CN Lactamase, β- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **91746-64-4D**, complexes with DD-peptidase **717919-90-9D**, complexes with DD-peptidase
RL: BSU (Biological study, unclassified); PRP (Properties); **BIOL (Biological study)**
(inhibitor; crystal structure of DD-peptidase/β - **lactamase** inhibitor complexes in relation to antibiotic design)
RN 91746-64-4 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 717919-90-9 HCAPLUS
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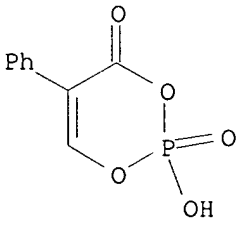

L49 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:55270 HCAPLUS
DN 138:233885
ED Entered STN: 24 Jan 2003
TI Inhibition of β **-Lactamases** by Monocyclic Acyl Phosph(on)ates
AU Kaur, Kamaljit; Adediran, S. A.; Lan, Martin J. K.; **Pratt, R. F.**
CS Department of Chemistry, Wesleyan University, Middletown, CT, 06459, USA
SO Biochemistry (2003), 42(6), 1529-1536
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)

IT 17838-69-6P, Ethyl 2-formyl-2-phenylacetate 40233-96-3P 501948-98-7P
501948-99-8P 501949-00-4P 501949-01-5P 501949-02-6P 501949-03-7P
501949-04-8P 501949-05-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)
IT 9000-81-1, Acetylcholinesterase 9025-82-5, Phosphodiesterase I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monocyclic acyl phosph(on)ates do not inhibit acetylcholinesterase and phosphodiesterase I)
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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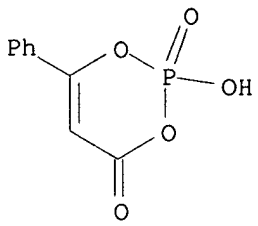
IT **9073-60-3, β -Lactamase 27238-11-5**
91746-64-4 229344-36-9
RL: BSU (Biological study, unclassified); **BIOL (Biological study)**
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)
RN 9073-60-3 HCAPLUS
CN Lactamase, β- (9CI) (CA INDEX NAME)

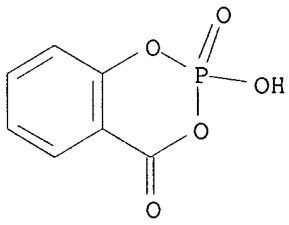
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 27238-11-5 HCAPLUS

CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, sodium salt (9CI) (CA INDEX NAME)



● Na

RN 91746-64-4 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 229344-36-9 HCAPLUS
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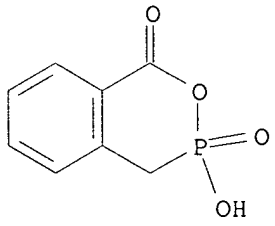
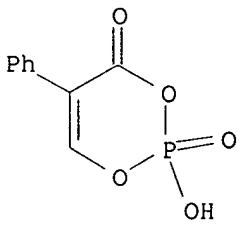


IT **501948-95-4P 501948-97-6P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)
(P99 and TEM-2 β **-lactamases** can be inhibited by monocyclic acyl phosph(on)ates by acylation of serine residue at active site)
RN 501948-95-4 HCAPLUS
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-5-phenyl-, 2-oxide, sodium salt (9CI) (CA INDEX NAME)



● Na

RN 501948-97-6 HCAPLUS
CN 6H-1,2-Oxaphosphorin-6-one, 2,3-dihydro-2-hydroxy-5-phenyl-, 2-oxide, compd. with N-cyclohexylcyclohexanamine (1:1) (9CI) (CA INDEX NAME)

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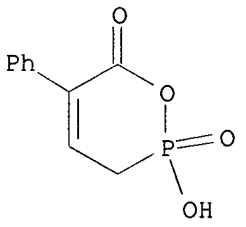
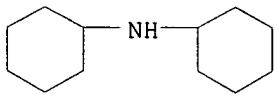
CRN 501948-96-5
CMF C10 H9 O4 P



CM 2

CRN 101-83-7
CMF C12 H23 N



L49 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:143282 HCAPLUS
DN 136:183941
ED Entered STN: 22 Feb 2002
TI Preparation of acyl phosphate and acyl phosphonate derivatives as inhibitors of **beta-lactamases** and DD-peptidases
IN **Besterman, Jeffrey M.; Rahil, Jubrail; Pratt, Rex**
PA Can.
SO U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 582,255.
CODEN: USXXCO

DT Patent
LA English
IC ICM C07F009-547
ICS C07F009-141; A61K031-66
INCL 514105000
CC 29-7 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): **1**, 7, 10, **63**
FAN.CNT 2

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PI	US 2002022607	A1	20020221	US 2001-797308	20010301 <--
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	WO 9933850	A1	19990708	WO 1998-US27518	19981223 <--
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	US 2005119233	A1	20050602	US 2003-628649	20030728 <--
PRAI	US 1997-68837P	P	19971224 <--		
	WO 1998-US27518	W	19981223 <--		
	US 2000-582255	A2	20000901 <--		
	US 2001-797308	A3	20010301 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2002022607	ICM	C07F009-547
	ICS	C07F009-141; A61K031-66
	INCL	514105000
US 2002022607	NCL	514/105.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
WO 9933850	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--
US 6608046	NCL	514/120.000; 423/302.000; 423/316.000; 558/079.000; 568/012.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A4; C07F009/6574A1 <--
US 2005119233	NCL	514/124.000
	ECLA	C07F009/09A9Q; C07F009/09B; C07F009/40C9Q; C07F009/6571L4; C07F009/6574A1; C07F009/6574A4 <--

OS MARPAT 136:183941
AB Acyl phosphates and acyl phosphonates, e.g. sodium benzoyl Ph phosphate (I), were prepared Thus, disodium Ph phosphate was reacted with benzoic anhydride to give I. The prepared compds. bind bacterial DD-peptidases, thus potentially acting both as β **-lactamase** inhibitors and as antibiotics. Biol. data are given.
ST lactamase inhibitor phosphonate phosphate prepn; antibiotic phosphonate phosphate prepn lactamase peptidase inhibitor; peptidase inhibitor phosphonate phosphate prepn; phosphonate prepn lactamase peptidase inhibitor; phosphate prepn lactamase peptidase inhibitor; antibacterial phosphonate phosphate prepn **beta lactamase** inhibitor
IT Antibacterial agents
Antibiotic resistance
Antibiotics
Human

(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT **9073-60-3** 9077-67-2
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(inhibitors; preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 50363-66-1P 68977-60-6P **91746-64-4P** 91929-16-7P
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341554-80-1P 341554-81-2P 341554-82-3P 341554-83-4P 341554-85-6P
341554-86-7P 341554-87-8P 341554-88-9P 341554-89-0P 341554-90-3P
383914-12-3P 383914-14-5P 400605-07-4P **400605-09-6P**
400605-11-0P 400605-14-3P 400605-16-5P 400605-18-7P 400605-21-2P
400605-23-4P 400605-25-6P 400605-27-8P 400605-29-0P
400605-31-4P 400605-32-5P 400605-34-7P 400605-36-9P 400605-42-7P
400605-43-8P 400605-44-9P 400605-47-2P 400605-69-8P
400605-71-2P
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 69-72-7, Salicylic acid, reactions 77-98-5, Tetraethylammonium hydroxide 93-97-0, Benzoic anhydride 98-88-4, Benzoyl chloride 500-98-1, Phenylacetylglycine 770-12-7, Phenyl dichlorophosphate 3279-54-7 7558-79-4, Disodium hydrogenphosphate 10025-87-3, Phosphorus oxychloride 55601-40-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT 383914-15-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

IT **9073-60-3**
RL: **BSU (Biological study, unclassified)**; **BIOL (Biological study)**
(inhibitors; preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

RN 9073-60-3 HCAPLUS
CN Lactamase, β- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **91746-64-4P 229344-36-9P 400605-09-6P 400605-23-4P 400605-71-2P**
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of **beta-lactamases** and DD-peptidases)

RN 91746-64-4 HCAPLUS
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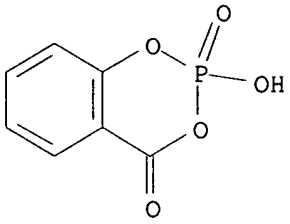
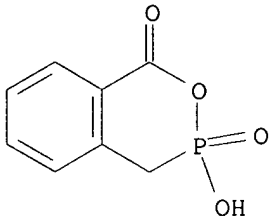


RN 229344-36-9 HCAPLUS
CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



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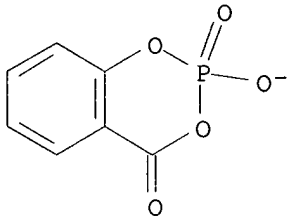

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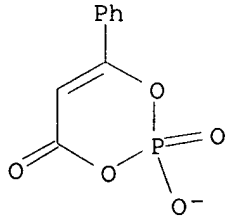
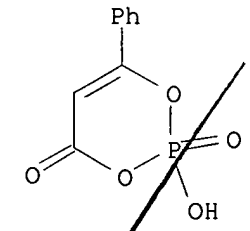


RN 400605-71-2 HCAPLUS
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



L49 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:731840 HCAPLUS
DN 136:33785
ED Entered STN: 08 Oct 2001
TI Mechanism of Inhibition of the Class C β -**Lactamase** of Enterobacter cloacae P99 by Cyclic Acyl Phosph(on)ates: Rescue by Return
AU Kaur, Kamaljit; Lan, Martin J. K.; **Pratt, R. F.**
CS Department of Chemistry, Wesleyan University, Middletown, CT, 06459, USA
SO Journal of the American Chemical Society (2001), 123(43), 10436-10443
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
CC 7-4 (Enzymes)
OS CASREACT 136:33785
AB As previously described (Pratt, R. F.; Hammar, N. J. J. Am. Chemical Society 1998, 120, 3004.), 1-hydroxy-4,5-benzo-2,6-dioxaphosphorinone(3)-1-oxide (salicyloyl cyclic phosphate) inactivates the class C β -**lactamase** of Enterobacter cloacae P99 in a covalent fashion. The inactivated enzyme slowly reverts to the active form. This paper shows that reactivation involves a recyclization reaction that regenerates salicyloyl cyclic phosphate rather than hydrolysis of the covalent intermediate. The inactivation, therefore, is a slowly reversible covalent modification of the active site. The thermodn. dissociation constant of the inhibitor from the inactivated enzyme is 0.16 μM. Treatment of the inactivated enzyme with alkali does not produce salicylic acid but does, after subsequent acid hydrolysis, yield one molar equivalent of lysinoalanine. This result proves that salicyloyl cyclic phosphate inactivates the enzyme by (slowly reversible) phosphorylation of the active site serine residue. This result contrasts sharply with the behavior of acyclic acyl phosphates which transiently inactivate the P99 . **beta.-lactamase** by acylation (Li, N.; Pratt, R. F. J. Am. Chemical Society 1998, 120, 4264.). This chemoselectivity difference is explored by means of mol. modeling. Rather counterintuitively, in view of the relative susceptibility of phosphates and phosphonates to nucleophilic attack at phosphorus, 1-hydroxy-4,5-benzo-2-oxaphosphorinanone(3)-1-oxide, the phosphonate analog of salicyloyl cyclic phosphate, did not appear to inactivate the P99 β -**lactamase** in a time-dependent fashion. It was found, however, to act as a fast reversible inhibitor (Ki = 10 μM). A closer examination of the kinetics of inhibition revealed that both on and off rates (9.8 + 103 s-1 M-1 and 0.098 s-1, resp.) were much slower than expected for noncovalent binding. This result strongly indicates that the inhibition reaction of the phosphonate also involves phosphylation of the active site. Hence, unlike the situation with bacterial DD-peptidases covalently inactivated by β-lactams, the P99 β -**lactamase** inactivated by the above cyclic acyl phosph(on)ates can be rescued by

return. Elimination of the recyclization reaction would lead to more effective inhibitors.

ST lactamase Enterobacter inhibition cyclic phosphonate; phosphate cyclic phosphorylation serine Enterobacter lactamase

IT Enterobacter cloacae
Enzyme functional sites
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT Enzyme kinetics
(of inhibition; cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 56-45-1, L-Serine, biological studies **9073-60-3**, β **-Lactamase 91746-64-4** 109099-32-3
RL: BSU (Biological study, unclassified); **BIOL (Biological study)**
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT **229344-36-9P** 379699-46-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 87-24-1 98-88-4, Benzoyl chloride 122-52-1, Triethyl phosphite 128-08-5, N-Bromosuccinimide 6881-57-8, Benzylphosphonic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT 7115-91-5P 79026-11-2P 101259-28-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

IT **850423-14-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Besterman, J; 1999 HCAPLUS
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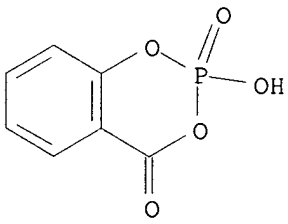
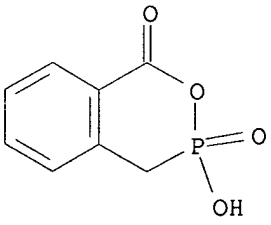
IT **9073-60-3, β -Lactamase 91746-64-4**
RL: BSU (Biological study, unclassified); **BIOL (Biological study)**
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)
RN 9073-60-3 HCAPLUS
CN Lactamase, β- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 91746-64-4 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



IT **229344-36-9P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)
RN 229344-36-9 HCAPLUS
CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



IT **850423-14-2P**

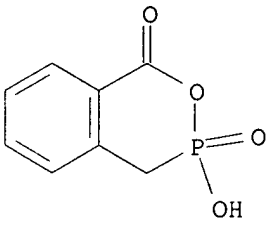
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclic acyl phosphates and phosphonates inhibit class C β **-lactamase** from E. cloacae P99 by reversible phosphorylation of active site serine)

RN 850423-14-2 HCAPLUS

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide, compd. with N-cyclohexylcyclohexanamine (1:1) (9CI) (CA INDEX NAME)

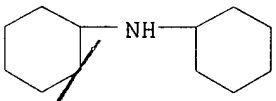
CM 1

CRN 229344-36-9
CMF C8 H7 O4 P



CM 2

CRN 101-83-7
CMF C12 H23 N



L49 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:460434 HCAPLUS

DN 131:82947

ED Entered STN: 28 Jul 1999

TI Novel β **-lactamase** and DD-peptidase inhibitors

IN **Besterman, Jeffrey M.; Rahil, Jubrail; Pratt, Rex**

PA **Methylgene, Inc., Can.**; Wesleyan University

SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C07F009-40
ICS A61K031-66; C07F009-6574; C07F009-6571; C07F009-09

CC 1-5 (**Pharmacology**)
Section cross-reference(s): 7, 10, 29

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9933850	A1	19990708	WO 1998-US27518	19981223 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,

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            KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
            MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
            TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
            FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
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    CA 2315821          AA    19990708    CA 1998-2315821        19981223 <--
    AU 9920945          A1    19990719    AU 1999-20945          19981223 <--
    AU 755799           B2    20021219
    EP 1042334          A1    20001011    EP 1998-965488         19981223 <--
    EP 1042334          B1    20020522
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    JP 2002503643       T2    20020205    JP 2000-526526         19981223 <--
    AT 217875           E     20020615    AT 1998-965488         19981223 <--
    ES 2178302          T3    20021216    ES 1998-965488         19981223 <--
    US 6608046          B1    20030819    US 2000-582255         20000901 <--
    US 2002022607       A1    20020221    US 2001-797308         20010301 <--
    US 6599889          B2    20030729
    US 2005119233       A1    20050602    US 2003-628649         20030728 <--
PRAI US 1997-68837P     P     19971224  <--
    WO 1998-US27518     W     19981223  <--
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CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 9933850       ICM    C07F009-40
                  ICS    A61K031-66; C07F009-6574; C07F009-6571; C07F009-09
 WO 9933850       ECLA   C07F009/09A9Q; C07F009/09B; C07F009/40C9Q;
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OS   MARPAT 131:82947
GI
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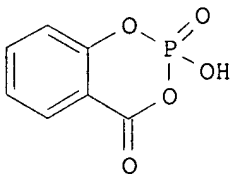


I

AB The invention provides novel β -**lactamase** inhibitors, which are structurally unrelated to the natural product and semi-synthetic β -**lactamase** inhibitors presently available, and which do not possess β-lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. The inhibitors also bind

bacterial DD-peptidases, thus potentially acting both a β -**lactamase** inhibitors and as antibiotics. β -**Lactamase** inhibition by the compds. and compds. such as I and PhCO2P(O)(O-)Me may have antibiotic properties, as evidenced by their inhibition of DD-peptidase.

ST phosphate lactamase peptidase inhibitor; phosphonate lactamase peptidase inhibitor; lactamase inhibitor phosphonate phosphate; peptidase inhibitor phosphonate phosphate

IT Antibiotic resistance
Antibiotics
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

IT **9073-60-3**, β -**Lactamase** 9077-67-2
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PROC (Process)
(inhibitors; phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

IT 50363-66-1P **91746-64-4P** 91929-16-7P 109099-32-3P **229344-36-9P** 229344-37-0P 229344-38-1P 229344-39-2P 229344-40-5P 229344-41-6P 229344-42-7P 229344-43-8P **229344-44-9P**
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP (Preparation); USES (Uses)
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

IT 69-72-7, reactions 93-97-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

IT **5381-98-6P** 83868-01-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Kazlauskas, R; J ORG CHEM 1985, V50(7), P1069 HCAPLUS
(2) Laird, R; J CHEM SOC PERKIN TRANS 1973, V2(10), P1434
(3) Li, N; BIOORG MED CHEM 1997, V5(9), P1783 HCAPLUS
(4) Li, N; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1998, V120(18), P4264 HCAPLUS
(5) Pratt, R; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1998, V120(13), P3004 HCAPLUS
(6) Rahil, J; BIOCHEM J 1991, V275(3), P793 HCAPLUS
(7) Song, Y; BIOORG MED CHEM LETT 1994, V4(10), P1225 HCAPLUS

IT **9073-60-3**, β -**Lactamase**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; **BIOL (Biological study)**; PROC (Process)
(inhibitors; phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

RN 9073-60-3 HCAPLUS

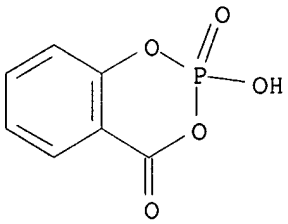
CN Lactamase, β- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

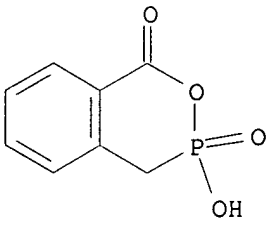
IT **91746-64-4P 229344-36-9P 229344-44-9P**
RL: **BAC (Biological activity or effector, except adverse)**; **BSU (Biological study, unclassified)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; **BIOL (Biological study)**; PREP

(Preparation); USES (Uses)
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

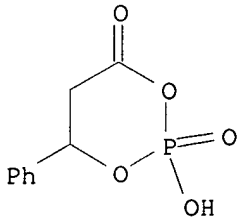
RN 91746-64-4 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 229344-36-9 HCAPLUS
CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)

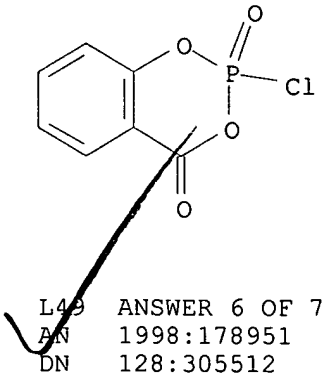


RN 229344-44-9 HCAPLUS
CN 1,3,2-Dioxaphosphorinan-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



IT **5381-98-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(phosphate and phosphonate β -**lactamase** and DD-peptidase inhibitors)

RN 5381-98-6 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



L49 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:178951 HCAPLUS
DN 128:305512
ED Entered STN: 27 Mar 1998
TI Salicyloyl Cyclic Phosphate, a "Penicillin-Like" Inhibitor of . **beta.-Lactamases**
AU **Pratt, R. F.**; Hammar, Ned J.
CS Chemistry Department, Wesleyan University, Middletown, CT, 06459, USA
SO Journal of the American Chemical Society (1998), 120(13), 3004-3006
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
CC 7-3 (Enzymes)
AB Salicyloyl cyclic phosphate (1-hydroxy-4,5-benzo-2,6-dioxaphosphorinanone (3)-1-oxide) was designed as a "penicillin-like" inhibitor of . **beta.-lactamases**. It was anticipated that, after nucleophilic attack on this mol. by the enzyme, the leaving group would remain tethered, and, as in the inhibition of DD-peptidases by penicillins, obstruct hydrolysis of the covalent intermediate back to free enzyme. The target mol., hitherto only reported as a transient intermediate, was prepared by hydrolysis of the cognate cyclic phosphoryl chloride and isolated and characterized as the dicyclohexylammonium salt. It proved to transiently inhibit the class C β - **lactamase** of Enterobacter cloacae P99, the class A TEM . **beta.-lactamase**, and also the DD-peptidase of Streptomyces R61. Most significantly, the half-lives of the complexes formed with these enzymes were 14, 140, and 340 min, resp. Thus, this cyclic phosphate represents a new class of mol. leading to inert complexes of β-lactam-recognizing enzymes.
ST prepn salicyloyl phosphate inhibitor **beta lactamase**
IT Enzyme kinetics
(of inhibition; preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β - **lactamases**)
IT **91746-64-4P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)
(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β **-lactamases**)
IT **9073-60-3, β -Lactamase** 9077-67-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β **-lactamases**)
IT **5381-98-6**
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bender, M; J Am Chem Soc 1963, V85, P3010 HCAPLUS
(2) Bruice, T; J Am Chem Soc 1995, V117, P12064 HCAPLUS
(3) Courvalin, P; J Antimicrob Chemother 1996, V37, P855 HCAPLUS
(4) Cremlyn, R; Phosphorus Sulfur 1980, V10, P333
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(14) Pratt, R; The Chemistry of β-Lactams 1992, P229 HCAPLUS
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(17) Rahil, J; Biochemistry 1992, V31, P5869 HCAPLUS
(18) Xu, Y; Biochemistry 1996, V35, P3595 HCAPLUS
(19) Zimmerle, C; Biochem J 1989, V258, P381 HCAPLUS

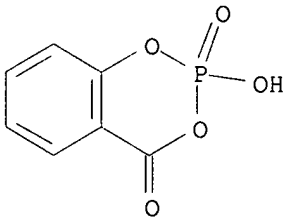
IT **91746-64-4P**

RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **BIOL (Biological study)**; PREP (Preparation)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)

RN 91746-64-4 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



IT **9073-60-3**, β -**Lactamase**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)

RN 9073-60-3 HCAPLUS

CN Lactamase, β- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

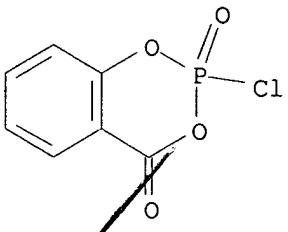
IT **5381-98-6**

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation and characterization of salicyloyl cyclic phosphate, a penicillin-like inhibitor of β -**lactamases**)

RN 5381-98-6 HCAPLUS

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



L48 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1981:619996 HCAPLUS
DN 95:219996
ED Entered STN: 12 May 1984
TI Synthesis of the o-carbamoylphenyl ester of thiamine monophosphate
AU Lettieri, G.; Brancaccio, G.; Larizza, A.; Viterbo, R.
CS Lab. Ric., Richardson-Merrell S.p.A., Naples, Italy
SO Bollettino Chimico Farmaceutico (**1981**), 120(5), 303-7
CODEN: BCFAAI; ISSN: 0006-6648
DT Journal
LA Italian
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): **1**
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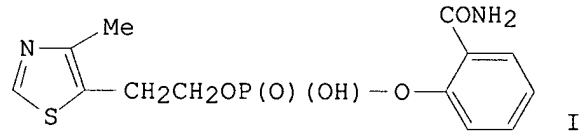

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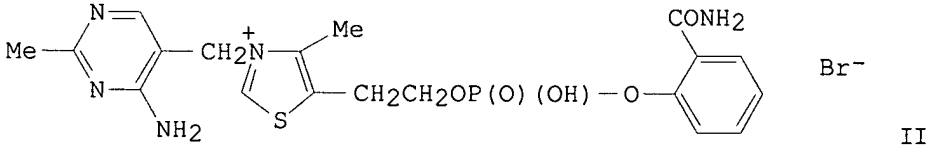
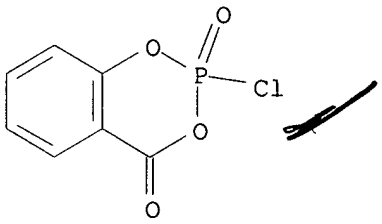


II

AB The thiazoleethanol ester I was converted to the title thiamine derivative (II). A mixture of I cyclohexylammonium salt, 2-methyl-4-amino-5-(bromomethyl)pyrimidine hydrobromide, and CHBr3 was stirred at 105° to give II, useful as an analgesic and antiinflammatory agent (no data).
ST thiamine phenylphosphate prepn analgesic; antiinflammatory thiamine phenylphosphate prepn
IT Analgesics
Inflammation inhibitors
(thiamine monophosphate derivative)
IT 7664-41-7, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation of O-(o-carboxyphenyl) phosphoric acid derivative by)
IT 2908-71-6
RL: PROC (Process)
(conversion of, to thiamine derivative)

IT 137-00-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of O-(o-carboxyphenyl) phosphoric acid derivative by)
IT **5381-98-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of, by (hydroxyethyl)thiazole derivative)
IT 79929-26-3P 79929-27-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conversion of, to thiamine derivative)
IT 79929-28-5P 79929-29-6P 79929-30-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT **5381-98-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of, by (hydroxyethyl)thiazole derivative)
RN 5381-98-6 HCAPLUS
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



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CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

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L50 4 S L24
L51 4 S L50 AND A61K/IPC

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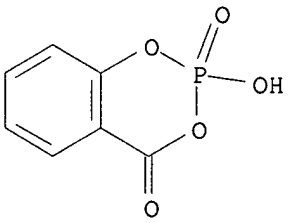
L51 ANSWER 1 OF 4 USPATFULL on STN
AN 2005:138583 USPATFULL
TI Acyl phosphonate inhibitors of beta-lactamases
IN Besterman, Jeffrey M., Baie D'Urfe, CANADA
Rahil, Jubrail, Dollard Des Ormeaux, CANADA
Pratt, Rex, Portland, CT, UNITED STATES
PI US 2005119233 A1 20050602
AI US 2003-628649 A1 20030728 (10)
RLI Division of Ser. No. US 2001-797308, filed on 1 Mar 2001, GRANTED, Pat. No. US 6599889 Continuation-in-part of Ser. No. US 2000-582255, filed on 1 Sep 2000, GRANTED, Pat. No. US 6608046 A 371 of International Ser. No.

WO 1998-US27518, filed on 23 Dec 1998
PRAI US 1997-68837P 19971224 (60)
DT Utility
FS APPLICATION
LREP KEOWN & ASSOCIATES, 500 WEST CUMMINGS PARK, SUITE 1200, WOBURN, MA, 01801, US
CLMN Number of Claims: 50
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1228
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel β-lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β-lactamase inhibitors presently available, and which do not possess a β-lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β-lactamase inhibitors and as antibiotics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **91746-64-4P 229344-36-9P 229344-44-9P**
(phosphate and phosphonate β-lactamase and DD-peptidase inhibitors)
RN 91746-64-4 USPATFULL
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



RN 229344-36-9 USPATFULL
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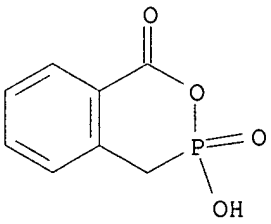

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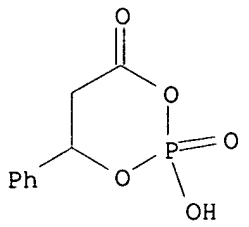
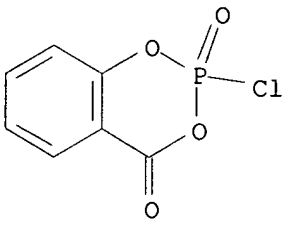


IT **5381-98-6P**
(phosphate and phosphonate β-lactamase and DD-peptidase inhibitors)
RN 5381-98-6 USPATFULL
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)



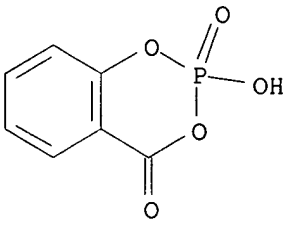
L51 ANSWER 2 OF 4 USPATFULL on STN
AN 2003:222100 USPATFULL
TI β-lactamase and DD-peptidase inhibitors
IN Besterman, Jeffrey M., Baie d'Urfe, CANADA
Rahil, Jubrail, Dollard des Ormeaux, CANADA
Pratt, Rex, Portland, CT, United States
PA MethylGene, Inc., St. Laurent, CANADA (non-U.S. corporation)
PI US 6608046 B1 20030819
WO 9933850 19990708
AI US 2000-582255 20000901 (9)
WO 1998-US27518 19981223
PRAI US 1997-68837P 19971224 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Solola, Taofiq
LREP Keown & Associates
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 848
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel β-lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β-lactamase inhibitors presently available, and which do not possess β-lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β-lactamase inhibitors and as antibiotics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **91746-64-4P 229344-36-9P 229344-44-9P**
(phosphate and phosphonate β-lactamase and DD-peptidase inhibitors)

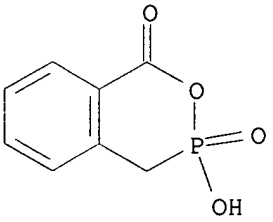
RN 91746-64-4 USPATFULL

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



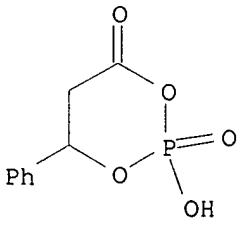
RN 229344-36-9 USPATFULL

CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



RN 229344-44-9 USPATFULL

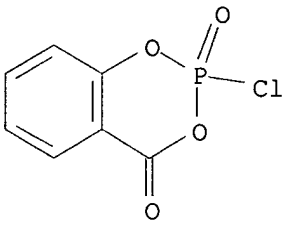
CN 1,3,2-Dioxaphosphorinan-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



IT **5381-98-6P**
(phosphate and phosphonate β-lactamase and DD-peptidase inhibitors)

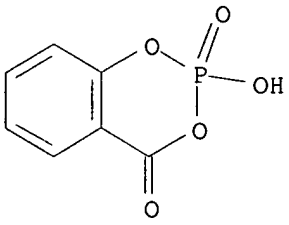
RN 5381-98-6 USPATFULL

CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-chloro-, 2-oxide (9CI) (CA INDEX NAME)

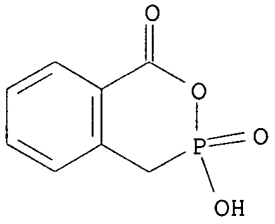


L51 ANSWER 3 OF 4 USPATFULL on STN
AN 2002:37887 USPATFULL
TI Acyl phosphonate inhibitors of beta-lactamases
IN Besterman, Jeffrey M., Baie D'Urfe, CANADA
Rahil, Jubrail, Dollard Des Ormeaux, CANADA
Pratt, Rex, Portland, CT, UNITED STATES
PI US 2002022607 A1 20020221
US 6599889 B2 20030729
AI US 2001-797308 A1 20010301 (9)
RLI Continuation-in-part of Ser. No. US 2000-582255, filed on 1 Sep 2000, PENDING A 371 of International Ser. No. WO 1998-US27518, filed on 23 Dec 1998, UNKNOWN
PRAI US 1997-68837P 19971224 (60)
DT Utility
FS APPLICATION
LREP HALE AND DORR, LLP, 60 STATE STREET, BOSTON, MA, 02109
CLMN Number of Claims: 50
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1242
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel β-lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β-lactamase inhibitors presently available, and which do not possess a β-lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β-lactamase inhibitors and as antibiotics.

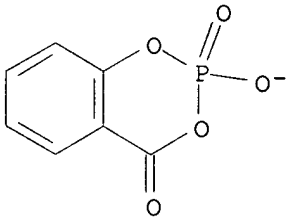
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **91746-64-4P 229344-36-9P 400605-09-6P 400605-23-4P 400605-71-2P**
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of beta-lactamases and DD-peptidases)
RN 91746-64-4 USPATFULL
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



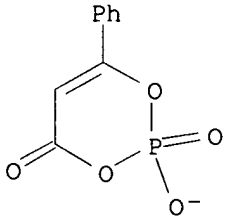
RN 229344-36-9 USPATFULL
CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



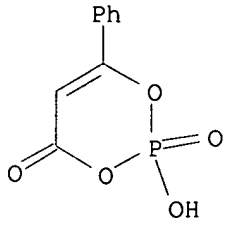
RN 400605-09-6 USPATFULL
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-23-4 USPATFULL
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)

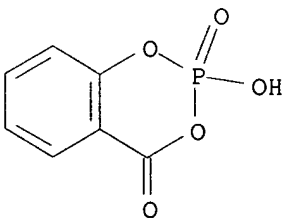


RN 400605-71-2 USPATFULL
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)

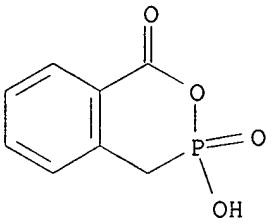


L51 ANSWER 4 OF 4 USPAT2 on STN
AN 2002:37887 USPAT2
TI Acyl phosphonate inhibitors of β-lactamases
IN Besterman, Jeffrey M., Baie d'Urfe, CANADA
Rahil, Jubrail, Dollard des Ormeaux, CANADA
Pratt, Rex, Portland, CT, United States
PA MethylGere, Inc., St. Laurent, CANADA (non-U.S. corporation)
PI US 6599889 B2 20030729
AI US 2001-797308 20010301 (9)
RLI Continuation-in-part of Ser. No. US 582255
PRAI US 1997-68837P 19971224 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Solola, Taofiq
LREP Keown & Associates
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1094
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel β-lactamase inhibitors, which are structurally unrelated to the natural product and semi-synthetic β-lactamase inhibitors presently available, and which do not possess a β-lactam pharmacophore. These new inhibitors are fully synthetic, allowing ready access to a wide variety of structurally related analogs. Certain embodiments of these new inhibitors also bind bacterial DD-peptidases, thus potentially acting both as β-lactamase inhibitors and as antibiotics.

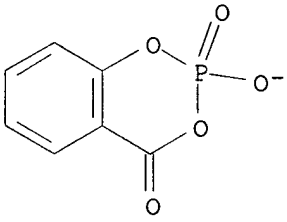
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **91746-64-4P 229344-36-9P 400605-09-6P**
400605-23-4P 400605-71-2P
(preparation of acyl phosphate and acyl phosphonate derivs. as inhibitors of beta-lactamases and DD-peptidases)
RN 91746-64-4 USPAT2
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide (9CI) (CA INDEX NAME)



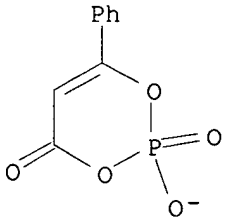
RN 229344-36-9 USPAT2
CN 1H-2,3-Benzoxaphosphorin-1-one, 3,4-dihydro-3-hydroxy-, 3-oxide (9CI) (CA INDEX NAME)



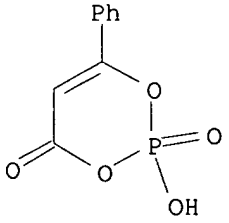
RN 400605-09-6 USPAT2
CN 4H-1,3,2-Benzodioxaphosphorin-4-one, 2-hydroxy-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-23-4 USPAT2
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide, ion(1-) (9CI) (CA INDEX NAME)



RN 400605-71-2 USPAT2
CN 4H-1,3,2-Dioxaphosphorin-4-one, 2-hydroxy-6-phenyl-, 2-oxide (9CI) (CA INDEX NAME)



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L4            75 S E3-E8,E11
               E RAHIL J/AU
L5            24 S E3-E6
               E PRATT R/AU
L6           520 S E3-E28
               E PRATT REX/AU
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               E METHYLGENE/PA,CS
L8            38 S E3-E10
               E METHYL GENE/PA,CS
               SEL RN L3

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L15          197 S L13 FUL
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L43           7 S L34,L40,L42
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